EP04/12060

REC'D 28 DEC 2004
WIPO PCT

PRV
PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

Intyg
Certificate

REGISTRERINGSVERKET • PATENT

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

(71) *Sökande* / *Applicant (s)* — *Lidds AB, Stockholm SE*

(21) *Patentansökningsnummer* / *Patent application number* — *0302782-8*

(86) *Ingivningsdatum* / *Date of filing* — *2003-10-22*

Stockholm, 2004-11-08

För Patent- och registreringsverket
For the Patent- and Registration Office

Hjördis Segerlund

Avgift
Fee 170:-

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

COMPOSITION FOR SUSTAINED DRUG DELIVERY

FIELD OF THE INVENTION

The present invention relates to novel compositions suitable for drug delivery of therapeutic substances to the human body or any other mammals. In particular, the compositions of the invention are applicable in the treatment of prostate cancer through targeted and local release of hormonal and anti-hormonal agents, including androgens with derivates (e.g. testosterone), antiandrogens (cyproteron, flutamide, hydroxy-flutamide, bicalutamide, nilutamide), oestrogens with derivates, anti-oestrogens (e.g. tamoxifen, toremifen), gestagens with derivates, anti-gestagens, oligonucleotides, progestagens, gonadotropin-releasing hormone analogues, gonadotropin inhibitors, adrenal and prostate enzyme synthesis inhibitors (such as α-reductase inhibitors), inhibitors of membrane efflux and membrane transport proteins (such as PSC 833, verapamil) other cytostatic agents, immune system modulators and angiogenesis inhibitors alone or in combination. It is also possible to include drug(s) from other pharmacological classes in combination in order to further enhance the efficacy and utility of the novel pharmaceutical composition. However, the compositions of the invention can also be explored for other drug delivery purposes regarding applied tissue(s) and/or used active drug substance(s).

With the compositions of the invention, local application in soft tissue of the drug delivery product containing the active drug(s), at the location of the tumour, and a sustained local release profile of the drug(s) over a suitable period of time, are made possible. Such local and sustained delivery of the therapeutic drug(s), alone or in combination, optimises the local concentration-time profile of the active compound(s) and their local pharmacological effect(s), and minimises the systemic exposure, reduces the spectrum of side effects, and hence increase the safety and utility of the novel pharmaceutical composition. The compositions may also be used for systemic sustained release drug delivery purposes regarding applied tissue(s) and/or used active drug substance(s).

BACKGROUND OF THE INVENTION

The principal application of the present invention is for treatment of prostate diseases, primarily cancer and prostate hyperplasia (enlarged prostate). Some background to this field is provided first.

Tumours can be divided into a malignant and non-malignant group. Cancers and Sarkomas are the two types of malignant tumours, characterised by a non-controlled cell growth, and by the ability to invade and seed metastasis.

For men prostate cancer is the most common type of cancer; it is today a leading lethal malignancy with increasing incidence worldwide. All prostate cancer patient develop a resistance to antihormonal treatments (a so called androgen-independent disease), which remains the main obstacle to improved life expectancy. Existing systemic hormonal treatments only improve survival with a few years.

The function of the prostate gland is to secrete the milky substance of seminal fluid. Before puberty, this function does not exist and the gland is very small. Unlike many organs the growth of the prostate gland continues throughout the lifespan of a man, often resulting in a benign prostatic hyperplasia of the gland.

The prostate is located anteriorly to the rectum. Above the prostate gland is the urinary bladder and below the urogenital diaphragm. The seminal vesicles form the ejaculatory ducts and enter the gland in a posterio-lateral direction and emerge in the urethra in approximately the middle of the gland. The gland is covered by a fibrotic capsule and has an elastic consistency.

The frequency of prostate cancer has stimulated the search for improved therapeutic agents and treatment procedures, e.g. novel anti-androgenic agents, prostate cancer gene therapy, immunotherapy. An important factor for a successful outcome of many of these new, or the more established therapeutic approaches, is ensuring sufficient local and sustained effect of the therapeutic substance within the tumour tissue, while minimising systemic effects.

Treatment options

The treatment options for early-stage prostate cancer can be grouped into four broad categories: observation (for elderly patients and those with co-morbidities), anti-cancer chemotherapy (often hormone or anti-hormone therapy), surgery (radical prostatectomy), and radiotherapy (external-beam radiotherapy, brachytherapy, i.e. local placement of radioactive sources, or both).

The prostate is a hormone-responsive organ; this is the basis for treatments that either reduce serum and intracellular testosterone or block the actions of this hormone. Many anti-hormonal agents act to inhibit production of or block the action of testosterone. Examples of hormonal or anti-hormonal agents are oestrogens, progestagens, gonadotropin-releasing hormone analogues,

adrenal and prostate enzyme synthesis inhibitors, inhibitors of membrane efflux and membrane transport proteins, gestagenes and antigestagenes, androgens and antiandrogens. Common is a combination of an antiandrogen with a gonadotropin-releasing hormone analogue to provide total blockade of androgens.

Disadvantages with present hormonal/anti-hormonal therapies of prostate cancer

Common side-effects of systemically administered hormonal/anti-hormonal therapies are hot flushes, loss of libido or erectile function, weight gain, gynaecomastia, liver inflammation, and osteoporosis. These troublesome side-effects remain major obstacles to hormonal dosing, and must be balanced against the long-term benefits.

The most commonly used oral antiandrogen therapy today is biclutamide (Casodex). It is used alone for early non-metastatic disease. The side effect spectrum of all clinically used antiandrogens is well-known and includes diarrhea, breast enlargement, nausea, impotence, decreased libido, abdominal pain, flatulence, tiredness, asthenia, osteoporosis and sweating, and a decreased quality of life.

These side effects of the anti-cancer chemotherapy are to a major extent due to high levels of the active drug in the systemic circulation and different tissues outside the cancer tissue in the prostate. Importantly, none of these side effects are related to, or mediated by, the local drug action in the prostate tissue.

Also alternative methods for treating prostate diseases have been developed. Some are based on the intramuscular or subcutaneous application of sustained drug delivery depot formulations containing the selected drug as one component (LHRH Agonists and Antagonists with systemic effects on the testosterone production). Also repeated intraprostatic and intralesional injection of therapeutic compounds has been described. These methods have the disadvantages of producing either prolonged systemic exposure to high doses of formulations, or to require repetitive injections over substantial periods of time, respectively.

In view of the methods described above for treatment of prostate cancer, there is a need for improved procedures and formulations to optimise the effects of hormonal/anti-hormonal and other anticancer agents. Such better treatments would reduce the need for surgery and radio-treatments, and minimise the spectrum of side-effects.

However, also the drug treatment of many other types of cancer as well as other diseases in soft tissue in humans and any other mammals would benefit from the sustained release formulation of the invention, both for local and systemic delivery.

Drug delivery systems based on bio-degradable carrier substances

A range of drug delivery systems for local sustained delivery therapy has been developed. Most of them are based on biodegradable polymers as carriers for the therapeutically active component. The most used bio-degradable polymers are polylactic acids (PLA) or polylactic-co-glycolide acids (PLGA). But also polyhydroxy acids, polyesters, polyothoesters, polyamides, polyanhydrides, blockpolymers, etc, have been evaluated. Polymer-drug systems may be applied as designed solid implants, mouldable pastes or micro-spheres, which suspended in a suitable liquid are injected into the blood vessel system.

A method and compositions for treating prostate cancer with polymer micro-spheres holding therapeutic substances is described in: Patent USA 6,277,391 B1, Aug 21, 2001.

Polyanhydrides for drug delivery are described in: Bio-erodible polyanhydrides for controlled drug delivery, US4891225, filed Jan 21 field 1986.

A system for local delivery of drugs for tumour treatment is described in: Controlled local delivery of chemotherapeutic agents for treating solid tumours, US5626862, filed Aug 2, 1994.

Commercial products based on degradable polymer drug delivery systems are: Lupron Depot, Zoladex, Norplan and Gliadel.

Also bio-degradable ceramic compositions are used for drug delivery purposes. In orthopaedics e.g. hydroxyapatite, calcium phosphate or calcium sulphate systems are used in the form of beads granules, scaffolds, pre-cured solid implants and mouldable in-situ curing pastes, both to provide mechanical stability at the site of a fracture, but also to leak therapeutic substances to the surroundings. Drugs that are commonly combined with ceramic implant materials in orthopaedics are antibiotics and bone growth factors.

SUMMARY OF THE INVENTION

In the drug treatment of cancer tumours and other diseases in soft tissue there is a need to improve their efficacy by simultaneous optimising of the clinical effect(s) and reduction of side-

effect(s). This is made possible by applying this drug delivery system with a sustained drug release rate(s) into different organs. This maybe used for local treatment or to give a prolonged plasma concentration-time profile (systemic treatment) of the drug(s) of choice.

Furthermore, there is a need for systems that can provide sustained and local delivery of therapeutic compounds to the tissues of the prostate gland and its surroundings, hence generate high local, and at the same time low systemic drug concentrations, and thereby increase the effectiveness of the therapeutic agents and reduce the risk of side-effects.

According to the invention, local therapy is achieved by applying a slow release formulation, here referred to as a treatment composition, containing one or several therapeutic agents. All drug(s) from various pharmacological classes included in the presented local drug delivery system will be given an amount effective to optimise the clinical effect(s) and reduce the side-effect(s).

The present invention provides a highly mouldable pasty or putty-like composition, which can be positioned with standard surgical instruments (needles, tubings, etc) at the selected site of the prostate gland by injection, e.g. through the urethra. Once positioned, the biodegradable composition solidifies and thereafter guarantees a local and controlled release of the therapeutic agent(s) for a prolonged period of time to the surrounding tissues.

The treatment composition of the invention is characterised by: Injectablility through established needles and tubing systems for minimally invasive positioning at the site of the tumour or other organs/tissues; in-situ solidification; a controlled release-time-profile; a high X-ray visibility which facilitates the precise positioning and the continued monitoring of the bio-degradation rate, as well as dose monitoring.

The present invention achieves this objective with the use of a treatment composition, which is defined in claim 1 and the further specifications of claims 2-8 and in claim 9 with further specifications in claims 10-13.

DETAILED DESCRIPTION OF THE INVENTION

The local drug delivery system of the invention is based on the concept that locally applied therapy provides more efficient therapeutic results and fewer side effects compared to systemic therapy. A suitable delivery system generates high local but low systemic drug concentrations.

Of prime interest to the invention are hormonal or antihormonal anticancer modalities such as flutamide, hydroxy-flutamide, cyproteron, nilutamide or bicalutamide directly in or in the vicinity of the prostate gland in humans and other mammals.

All drug(s) from various pharmacological classes included in the presented local drug delivery system will be given an amount effective to optimise the clinical effect(s) and reduce the side-effect(s).

Examples of active drug substances from various pharmacolocial classes for the use in the present context include e.g. antibacterial agents, antihistamines and decongestants, anti-inflammatory agents, antiparasitics, antivirals, local anaesthetics, antifungals, amoebicidals or trichomonocidal agents, analgesics, antianxiety agents, anticlotting agents, antiarthritics, antiasthmatics, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antiglaucoma agents, antimalarials, antimicrobials, antineoplastics, antiobesity agents, antipsychotics, antihypertensives, auto-immune disorder agents, anti-impotence egents, anti-Parkinsonism agents, anti-Alzheimers agents, antipyretics, anticholinergics, anti-ulcer agents, anorexics, beta-blockers, beta-2 agonists, blood glucose-lowering agents, bronchodilators, agents with effect on the central nervous system, cardiovascular agents, cognitive enhancers, contraceptives, cholesterol-reducing agents, agents against dyslipidemia, cytostatics, diuretics, germicidals, H-2 blockers, hormonal agents, anti-hormonal agents, hypnotic agents, inotropics, muscle relaxants, muscle contractants, physic energizers, sedatives, sympathomimetics, vasodilators, vasoconstrictors, tranquilizers, electrolyte supplements, vitamins, uricosurics, cardiac glycosides, membrane efflux enhbitors, membrane transport protein inhibitors, expectorants, purgatives, contrast materials, radiopharmaceuticals, imaging agents, peptides, enzymes, growth factors, vaccines, mineral traceelements, etc.

The therapeutically, prophylactically and/or diagnostically active drug substance(s) may also be in the form of a pharmaceutically acceptable salt, solvate or complex thereof or in any suitable crystalline or amorphous form or it maybe in the form of a prodrug.

Apart from carrying the therapeutic agent, the treatment composition is such that it also provides a property profile including:

a viscosity allowing injectability through clinically used standard syringes, needles, tubing systems and cannulae for application of the treatment composition in the selected tissues;

in-situ solidification properties providing increased mechanical and chemical resistance after application at the selected site to make the implanted volume stay constrained and to degrade slowly over time;

a controlled bio-degradation rate of the solidified implant, and a local controlled release of the therapeutic agent or combination of agents over time, leading to a local concentration-time profile of the active drug(s) within the desired therapeutic window in the relevant tissues;

a radio-opacity that makes it visible with standard radioscopy methods. Radioscopy facilitates the accurate application of the treatment composition at the selected site, as well as the continuous monitoring of the bio-degradation rate for individualised dosing. Radio-opaque treatment compositions can also be used to increase the accuracy of radiation treatment. This opens for the possibility to combine adjuvant/neo-adjuvant local hormone and anti-hormone treatment(s) with a high precision external beam radiotherapy with or without a brachy boost.

The treatment composition delivers the therapeutic agent in such a way that the local concentration is kept within the therapeutic window for a prolonged period of time. For hydroxyflutamide, this therapeutic concentration is within the interval 0.05 – 5.0 μM and the treatment time for one dose at least 3 months.

The therapeutic agent may be implanted into the prostate tissue through the urethra by conventional cystoscopy or other techniques for injections/implantation, such as ultrasound, MR (magnetic resonance), X-ray, CT (computer tomography), manual guidance through the rectum, etc.

The treatment response may be monitored by assaying PSA (prostate specific antigen) in plasma (a well-established bio-marker for this disease), i.e. the same diagnostic systems used in routine practice in the management and follow-up of patients with prostate cancer. If a local treatment fails to lower the PSA level, the risk of metastatic tissue increases.

In contrast to prior art systems and products, the composition of the present invention, further described below, provides the attractive properties of injectabilty and in-vivo curing, which facilitates the accurate local positioning of the composition with simple tools. Also the treatment composition possesses radio-opacity without any radio-contrast additives.

The present invention utilises the inherent properties of hydrating cements. Hydrating cements are ceramic materials that solidify as a result of chemical reactions between a ceramic powder and water. The most explored hydrating cements are Portland cement (primarily calcium silicates), calcium sulphates (the main component of gypsum), and calcium phosphates (including hydroxyapatite, the hard phase of bony tissues). The hydrating cements are very hydrophilic and are used as fine-grained powders, which are mixed with water to achieve pastes of desired viscosities.

As the powder is mixed with water, chemical processes involving the dissolution of the powder grains in the water, followed by precipitation of crystallites of solid hydrates, takes place. The hence formed hydrates forms the binding phase in the formed solid material. The hydration process and thereby the properties of the hydrate materials is controlled by additives. By a suitable selection of additives properties such as rheology of the non-solidified paste, the curing rate, and the mechanical properties of the solidified material can be steered.

Examples of clinical products based on hydrating cements are dental fillings, root fillings and orthopaedic cements for fracture treatment.

Resorbable calcium phosphate based ceramics are described in US 6,027,742,

biodegradable cements are described inWO 95/13835, and

micro-spheres based on calcium phosphate are described in WO 98/43558.

In contrast to known compositions comprising hydrating cements, the composition of the present invention explores the demonstrated sustained release profile for hormonal, anti-hormonal anti-cancer pharmaceutical agents and/or drugs from other pharmacological classes to soft tissues and organs and benefits from injectability, in-vivo solidification, radio-opacity and the toxicologically favourable components of the treatment composition. The treatment composition of the present invention does not have the co-function of enhancing healing by mechanical stabilisation or by favouring hard tissue regeneration.

The rate of bio-degradation of hydrating cements depends on a range of factors, such as porosity and water content of the hydrates. Different hydrating cements are very different in their inherent chemical stability and degradation rate, calcium sulphates are generally considered as quickly degradable in body tissues, whereas hydrated calcium silicates are much more stable.

The treatment composition

The treatment composition of the invention fulfils the above described property profile.

In its most simple form the treatment composition of the invention consists exclusively of one or several therapeutic agents, together with an hydrating cement mixture which provides the solidification characteristics and the radio-opacity, and water as the sole solvent.

The most preferred therapeutic agent, or combination of agents is a hormonal or antihormonal therapy, primarily with cyproteron, flutamide, hydroxyflutamide, bicalutamide, nilutamide.

The invention is also applicable to therapeutic agents in a abroad sense, including androgens with derivates (e.g. testosterone), antiandrogens (cyproteron, flutamide, hydroxyflutamide, bicalutamide, nilutamide), oestrogens with derivates, anti-oestrogens (e.g. tamoxifen, toremifen), gestagens with derivates, antigestagens, oligonucleotides, progestagens, gonadotropin-releasing hormone analogues, gonadotropin inhibitors, adrenal and prostate enzyme synthesis inhibitors (such as α-reductase inhibitors), membrane efflux and membrane transport proteins (such as PSC 833, verapamil) other cytostatic agents, immune system modulators and angiogenesis inhibitors alone or in combination.

However, the invention also includes any other suitable pharmaceutical agents applied in soft tissues or organs for local or systemic sustained drug release. The sustained drug release compositions or the invention can also be explored in other treatments e.g.: pain, neurological diseases (Alzheimer, Parkinson), autoimmune diseases, immunological diseases, and diseases responding to immunological and immunomodulating therapy (hepatitis, MS, tumours), infections, inflammations, cardiovascular diseases (including blood pressure), hematopoietic, anticoagulant, thrombolytic and antiplatelet diseases, chemotherapy of parasitic infections, microbial diseases and neoplastic diseases, hypercholesterolemia, dyslipidemia, hematopoetic diseases, respiratory diseases (asthma, chronical lung obstruction) diseases of the kidney, gastrointestinal diseases, liver diseases, hormonal disruption, replacement and substitution, vitamins replacement and substitution. Examples of active drug substances from various

pharmacolocial classes for the use in the present clinical context include e.g. antibacterial agents, antihistamines and decongestants, anti-inflammatory agents, antiparasitics, antivirals, local anaesthetics, antifungals, amoebicidals or trichomonocidal agents, analgesics, antianxiety agents, anticlotting agents, antiarthritics, antiasthmatics, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antiglaucoma agents, antimalarials, antimicrobials, antineoplastics, antiobesity agents, antipsychotics, antihypertensives, auto-immune disorder agents, anti-impotence egents, anti-Parkinsonism agents, anti-Alzheimers agents, antipyretics, anticholinergics, anti-ulcer agents, anorexics, beta-blockers, beta-2 agonists, blood glucose-lowering agents, bronchodilators, agents with effect on the central nervous system, cardiovascular agents, cognitive enhancers, contraceptives, cholesterol-reducing agents, agents against dyslipidemia, cytostatics, diuretics, germicidals, H-2 blockers, hormonal agents, anti-hormonal agents, hypnotic agents, inotropics, muscle relaxants, muscle contractants, physic energizers, sedatives, sympathomimetics, vasodilators, vasoconstrictors, tranquilizers, electrolyte supplements, vitamins, uricosurics, cardiac glycosides, membrane efflux inhbitors, membrane transport protein inhibitors, expectorants, purgatives, contrast materials, radiopharmaceuticals, imaging agents, peptides, enzymes, growth factors, vaccines, mineral trace elements, etc.

The therapeutically, prophylactically and/or diagnostically active drug substance(s) may also be in the form of a pharmaceutically acceptable salt, solvate or complex thereof or in any suitable crystalline or amorphous form or it maybe in the form of a prodrug.

All drug(s) included in the presented local drug delivery system will be given an amount effective to optimise the clinical effect(s) and reduce the side-effect(s).

In its most basic form, the preferred hydrating cement of the treatment composition are: calcium sulphates and calcium phosphates, alone or in combinations. However, also calcium carbonates, calcium flourides and calcium silicates, alone or in combination, are relevant to the invention. In a more general form of the invention, the calcium of these ceramics may be replaced by magnesium or barium. Barium-based compounds increase the radio-opacity of the composition.

The treatment composition is steered to solidify within a time span of 5 to 20 minutes after final mixing to a solid body that resists the movements of the surrounding tissues and the flow of body fluids through the surrounding tissues.

The hydraulic component is added to the treatment composition in the form of a fine-grained powder, the grain size of which is below 100 µm. Most preferably the majority of the powder

grains are below 10 μm in diameter.

Any concentration of hydrated cement in the treatment composition falling between 10 and 99 vol.%, as measured on the solidified implant, is of relevance to the invention. Most preferably the solidified treatment composition contains between 70 and 95 vol. % of hydrated ceramic.

Optionally, the therapeutic agents are mixed with a bio-degradable polymeric substances such as: polylactic acid, polyglycolic acid, poly(lactic-co-glycolic) acid, polyanhydrides, blockpolymers, poly(orthoesters), poly(p-dioxanone), poly(alpha hydroxy butyric acid), and their co-polymers with polyethylene oxide or polypropylene oxide, and any mixtures thereof. The purpose of these polymer additives is to control the biodegradation rate and the drug release rate.

In a general form of the invention any bio-degradable polymeric additive, which may serve as carrier for a therapeutic agent is of relevance.

Optionally, the treatment composition of the invention may also contain non-hydrating ceramic and metallic additives. The purpose of such additional component is increased radio-opacity, improved mechanical strength or solidification rate control. Established radio-opacity additives are barium salts or metals such as gold, zirconium or tantalum and their oxides.

Optionally, the treatment composition of the invention also contains rheology control additives such as poly-carboxylic acids or poly-acrylic acids; methyl cellulose, dextran or hyaluronic acid.

The treatment composition contains water as principal solvent.

Optionally, the treatment composition may also contain a bio-adhesive component, such as suitable polymer, which helps the therapeutic agent to stay adhered to the surrounding tissue over a prolonged period of time.

EXAMPLE

Sustained release pharmaceutical dosage forms of calcium sulphate semi-hydrate ($CaSO_4 \cdot 1/2H_2O$, CS), water and hydroxyflutamide (HF) were prepared as a pellet form with a size of diameter 4 mm and thickness 1.0 mm. The release rate (amount over time) of HF in four compositions were tested:

Calcium sulphate with 20 % water and 8 % of HF by weight;
Calcium sulphate with 40 % water and 8 % of HF by weight;
Calcium sulphate with 20 % water and 8 % of HF and 10% of cellulose (avicel) by weight; and
Calcium sulphate with 20 % water and 8 % of HF and 30% of cellulose by weight.

Each pellets was incubated individually in tubes containing10 ml of saline solution (a simulated extracellular body fluid at pH 7.4 and 37 °C for in a water bath for a total of 14 days. A sample of 0.5 ml was taken every 24 hours and the volume was replaced with 0.5 ml of fresh saline solution. The concentration of HF in the saline solution was measured in each sample with a specific and validated HPLC-method with UV-detection. The volume of saline was kept constant at 10 ml. The sustained release of HF over a 14 days period is illustrated in Figure 1.

CLAIMS

1. The use of a composition, which comprises
at least one therapeutic agent,
at least one bio-degradable hydrating cement, and
an aqueous liquid,
for the manufacture of an injectable and in vivo-solidifying pharmaceutical formulation for sustained release of therapeutic agents in soft tissue.

2. The use as in claim 1, wherein the at least one therapeutic agent is an anti-cancer agent.

3. The use as in claim 2, wherein the anti-cancer agent is an androgen or a derivative thereof, an antiandrogen, an oestrogen or a derivative thereof, an anti-oestrogen, a gestagen or a derivative thereof, an antigestagen, an oligonucleotide, a progestagen, a gonadotropin-releasing hormone analogue, a gonadotropin inhibitor, an adrenal and prostate enzyme inhibitor, a membrane efflux and membrane transport protein, an immune system modulator, or an angiogenesis inhibitor,.

4. The use as in claim 3, wherein the antiandrogen is flutamide, hydroxy-flutamide, cyproteron, nilutamide or bicalutamide.

5. The use as in claim 3, wherein the at least one anti-cancer agent is a combination of an antiandrogen and a gonadotropin-releasing hormone analogue.

6. The use as in claim 1, wherein the at least one bio-degradable hydrating cement is a calcium sulphate, a calcium phosphate, a calcium carbonate, a calcium fluoride, a calcium silicate, a magnesium sulphate, a magnesium phosphate, a magnesium carbonate, a magnesium fluoride, a magnesium silicate, a barium sulphate, a barium phosphate, a barium carbonate, a barium fluoride, or a barium silicate.

7. The use as in claim 1, wherein the at least one bio-degradable hydrating cement is in the form of a powder.

8. The use as in claim 7, wherein the cement powder has a grain size below 100 μm in diameter.

9. The use as in claim 7, wherein the cement powder has a grain size below 10 µm in diameter.

10. The use as in claim 1, wherein the composition further comprises at least one biodegradable polymer.

11. The use as in claim 10, wherein the at least one bio-degradable polymer additive is a polylactic acid, a polyglycolic acid, a poly(lactic-co-glycolic) acid, a poly(orthoester), a poly(p-dioxanone), or a poly(alpha hydroxy butyric acid), or a co-polymer thereof with polyethylene oxide or polypropylene oxide, or a polyanhydride.

12. The use as in claim 10, wherein the bio-degradable polymer is in the form of grains or micro-spheres.

13. The use as in claim 12, wherein the grains or micro-spheres have a size below 500 µm in diameter.

14. The use as in any of claims 1-13, wherein the composition further comprises at least one non-immune response generating metallic additive and/or at least one inert ceramic additive.

15. An injectable and in vivo-solidifying composition, which comprises
at least one therapeutic agent,
at least one bio-degradable hydrating cement,
at least one biodegradable polymer, and
an aqueous liquid.

16. The composition as in claim 15, wherein the at least one therapeutic agent is an anti-cancer agent.

17. The composition as in claim 16, wherein the anti-cancer agent is an androgen or a derivative thereof, an antiandrogen, an oestrogen or a derivative thereof, an anti-oestrogen, a gestagen or a derivative thereof, an antigestagen, an oligonucleotide, a progestagen, a gonadotropin-releasing hormone analogue, a gonadotropin inhibitor, an adrenal and prostate enzyme inhibitor, a membrane efflux and membrane transport protein, an immune system modulator, or an angiogenesis inhibitor,.

18. The composition as in claim 17, wherein the antiandrogen is flutamide, hydroxy-flutamide, cyproteron, nilutamide or bicalutamide.

19. The composition as in claim 17, wherein the at least one anti-cancer agent is a combination of an antiandrogen and a gonadotropin-releasing hormone analogue.

20. The composition as in claim 15, wherein the at least one bio-degradable hydrating cement is a calcium sulphate, a calcium phosphate, a calcium carbonate, a calcium fluoride, a calcium silicate, a magnesium sulphate, a magnesium phosphate, a magnesium carbonate, a magnesium fluoride, a magnesium silicate, a barium sulphate, a barium phosphate, a barium carbonate, a barium fluoride, or a barium silicate.

21. The composition as in claim 15, wherein the at least one bio-degradable hydrating cement is in the form of a powder.

22. The composition as in claim 21, wherein the cement powder has a grain size below 100 μm in diameter.

23. The composition as in claim 21, wherein the cement powder has a grain size below 10 μm in diameter.

24. The composition as in claim 15, wherein the at least one bio-degradable polymer additive is a polylactic acid, a polyglycolic acid, a poly(lactic-co-glycolic) acid, a poly(orthoester), a poly(p-dioxanone), or a poly(alpha hydroxy butyric acid), or a co-polymer thereof with polyethylene oxide or polypropylene oxide, or a polyanhydride.

25. The composition as in claim 15, wherein the bio-degradable polymer is in the form of grains or micro-spheres.

26. The composition as in claim 15, wherein the grains or micro-spheres have a size below 500 μm in diameter.

27. The composition as in any of claims 15-26, which further comprises at least one non-immune response generating metallic additive and/or at least one inert ceramic additive.

Abstract

The present invention relates to the use of a composition, which comprises at least one therapeutic agent, at least one bio-degradable hydrating cement, and an aqueous liquid, for the manufacture of an injectable and in vivo-solidifying pharmaceutical formulation for sustained release of therapeutic agents in soft tissue. The invention also relates to an injectable and in vivo-solidifying composition, which comprises at least one therapeutic agent, at least one bio-degradable hydrating cement, at least one biodegradable polymer, and an aqueous liquid.

Figure 1.

Release curves over time of hydroxyflutamide (HF) from four pharmaceutical compositions which were incubated in saline solution (a simulated extracellular body fluid) at pH 7.4 and 37 °C for 14 days. The compositions of the sustained pharmaceutical formulations are given below:
H: 20 % water, 8 % HF, rest calcium sulphate as measured by weight.
M: 40 % water, 8 % HF, rest calcium sulphate as measured by weight.
106: 20 % water, 8 % HF, 10% of cellulose, rest calcium sulphate as measured by weight.
306: 20 % water, 8 % HF, 30% of cellulose, rest calcium sulphate as measured by weight.